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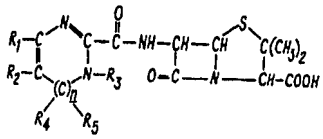
(54) PENICILLANIC AND CEPHALOSPORANIC ACID DERIVATIVES

(71) We, KONINKLIJKE NEDERLANDSCHE GIST-EN SPIRITUS-FABRIEK N.V., a Dutch Body Corporate of 1, Wateringseweg, Delft, The Netherlands, do hereby declare this invention to be described in the following statement:—

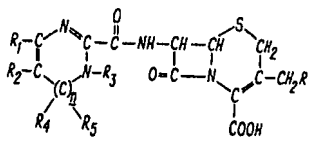
This invention relates to new therapeutically useful penicillanic and cephalosporanic acid derivatives, to a process for their preparation and pharmaceutical compositions containing them.

The new penicillanic and cephalosporanic acid derivatives of the present invention are those compounds of the general formulae



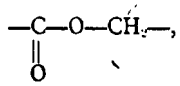
(I)

and



(II)

(wherein R represents a hydrogen atom, a hydroxy group or a lower alkanoyloxy group, or the grouping $-CH_2R$ and the carboxy group in formula (II) are linked together to form a lactone group, i.e.



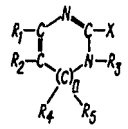
R_1 and R_2 are the same or different and each represents a hydrogen atom, a lower alkyl or lower alkoxy group, a cycloalkyl group of 5 to 8 carbon atoms (preferably cyclopentyl, cyclohexyl or cycloheptyl), a phenyl or phenoxy group, or a chlorine or fluorine atom, or R_1 and R_2 and the carbon atoms to which they are attached collectively form a phenyl group or a cycloalkylene group (preferably cyclohexenylene) with at least one double bond therein, the phenyl or cycloalkylene group optionally carrying one or more substituents, for example a chlorine atom or a lower alkyl or a lower alkoxy group, R_3 represents a hydrogen atom, a lower alkyl, vinyl or allyl group, a cycloalkyl group of 5 to 8 carbon atoms (preferably cyclopentyl, cyclohexyl or cycloheptyl), a phenyl(lower)alkyl (preferably benzyl) or phenyl group optionally carrying one or more substituents on the ring selected from lower alkyl and

lower alkoxy groups and the chlorine atom, R_4 and R_5 are the same or different and each represents a hydrogen atom or a lower alkyl group or R_4 and R_5 together represent a keto oxygen atom, and n is zero or 1) and their alkali metal, alkaline earth metal and amine salts. The term "lower" as applied herein to alkanoyloxy, alkyl and alkoxy groups means that the group contains at most 4 carbon atoms, for example, acetoxy in respect of lower alkanoyloxy groups, and methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy and butoxy in respect of lower alkyl and lower alkoxy groups.

It will be appreciated that when in formulae (I) and (II) R_1 and R_2 together with the carbon atoms to which they are attached represent a phenyl group, the heterocyclic group attached to the carbamoyl radical on the penicillanic or cephalosporanic nucleus will be a benzimidazol-2-yl ($n=0$) or quinazolin-2-yl ($n=1$) group.

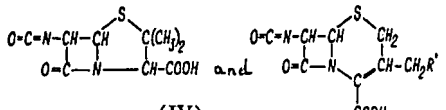
The presently preferred class of compounds is that in which in general formulae (I) and (II) R_1 and R_2 both represent hydrogen atoms or one represents a hydrogen atom and the other a chlorine atom, or R_1 and R_2 and the carbon atoms to which they are attached collectively form a phenyl group unsubstituted or substituted by a lower alkyl (preferably methyl or ethyl) or lower alkoxy (preferably methoxy or ethoxy) group, R_3 represents a hydrogen atom, a lower alkyl (preferably methyl or ethyl) or vinyl group, or a phenyl or benzyl group unsubstituted or carrying on the phenyl ring a lower alkyl (preferably methyl or ethyl) or lower alkoxy (preferably methoxy or ethoxy) group, and more particularly when n is 1 those compounds in which R_4 and R_5 each represent a hydrogen atom or R_4 and R_5 together represent a keto oxygen atom, and alkali metal, alkaline earth metal and amine salts of such compounds.

The new compounds of general formulae (I) and (II) are prepared, according to a feature of the invention, by the process which comprises reacting a heterocyclic compound of the general formula:



(III)

wherein R_1, R_2, R_3, R_4, R_5 and n are as hereinbefore defined and X represents a lithium atom or a magnesium chloride or magnesium bromide (i.e. —MgCl or —MgBr) group, with an ester of 6-isocyanato-penicillanic acid, or an ester or lactone of 7-isocyanato-cephalosporanic acid, the two acids having the formulae:



(IV) and (V)

respectively (wherein R′ is a hydrogen atom, a lower alkanoyloxy group or a protected hydroxy group) and hydrolysing the resulting organo-metal intermediate product to remove the metal atom and, when present, the esterifying group protecting the carboxy group and, when present, the group protecting the hydroxy group and, if desired, converting by methods known *per se* a penicillanic acid or cephalosporanic acid thus obtained into its alkali metal, alkaline earth metal or amine salt. Preferably the group protecting the carboxy radical, or hydroxy radical when present, in the 6-isocyanato-penicillanic or 7-isocyanato-cephalosporanic reactant is a tri(lower)-alkylsilyl or di(lower)alkylsilyl group, and more particularly trimethylsilyl, which can readily be removed from the intermediate product by hydrolysis.

6-Isocyanato-penicillanic acid and derivatives thereof are described and claimed in British Patent Specification No. 1,268,536. 7-Isocyanato-cephalosporanic acid and derivatives thereof are described and claimed in our copending Patent Application No. 61842/69 (Serial No. 1,341,827).

The process may be carried out in the following two ways:—

(1) A fairly concentrated solution of a suitable organo-metal reagent, e.g. n-butyl-

lithium in hexane, is added drop-wise and with stirring to a solution of the appropriate heterocyclic compound of formula (III) with X representing a hydrogen atom (for example and imidazole, benzimidazole, 3,4-dihydroquinazoline or quinazol-4-one) in an aprotic dipolar solvent, e.g. tetrahydrofuran, at a low temperature, e.g. −40° to −80° C., and stirring of the mixture is continued. Next, a solution of the isocyanate in an organic solvent, e.g. toluene or tetrahydrofuran, is added drop-wise at a low temperature, e.g. about −80° C., and the reaction mixture is thoroughly stirred. The organo-metal intermediate product is hydrolysed and finally the product of formula (I) or (II) is isolated from the reaction mixture by application of known procedures.

This method involves the use of a polar reaction medium in which, even at low temperatures, the reactants are mainly in solution.

(2) A solution of a complex of a suitable organo-metal reagent, preferably n-butyllithium, and an N,N,N',N' - tetrasubstituted - alkylene - diamine, e.g. N,N,N',N'-tetramethylethylenediamine, in an apolar solvent or solvent mixture, e.g. hexane-petroleum ether, is added to a solution or suspension of a heterocyclic compound of formula (III), X represents a hydrogen atom, in an apolar or slightly polar solvent, e.g. toluene, at a low temperature, e.g. −40° to −80° C., after which a solution of the isocyanate in toluene is introduced. The reaction mixture is then treated with water and the product of formula (I) or (II) is isolated from the reaction mixture by the application of known procedures.

In many cases both methods can be employed but the second is preferred because the reactivity of the organo-metal reagent (e.g. butyllithium) is specifically directed to carbon-hydrogen bonds in the case of heterocyclic starting materials carrying substituents which can easily be replaced or may add to the reagent under mild conditions, such as when ester groups are present.

The heterocyclic compounds of formula (III) may be prepared using known procedures by reacting a suitable organo-lithium or magnesium compound, e.g. n-butyllithium, ethylmagnesium bromide or isopropylmagnesium chloride (preferably n-butyllithium), with the appropriate heterocyclic compound in which X is hydrogen.

The new penicillanic and cephalosporanic acid derivatives conforming to general formulae (I) and (II) and their alkali metal, alkaline earth metal and amine salts have antibiotic properties which make them useful as medicines for men and animals and as additives in animal feed. They are particularly active against gram positive microorganisms.

Typical compounds of the invention are those illustrated in the Examples which follow hereinafter, i.e. 6 - (1 - methyl - imidazol - 2 - yl) - carbonamido - penicillanic acid (I), 6 - (1 - benzyl - imidazol - 2 - yl)carbonamido - penicillanic acid (II), 6 - (1 - benzyl - benzimidazol - 2 - yl)carbonamido - penicillanic acid (III), 6 - (1 - phenyl - 5 - methoxy - benzimidazol - 2 - yl) - carbonamido - penicillanic acid (IV), 6 - (benzimidazol - 2 - yl)carbonamido - penicillanic acid (V), 6 - (5 - chloro - 1 - methyl - imidazol - 2 - yl)carbonamido - penicillanic acid (VI), 6 - (3 - benzyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl) - carbonamido - penicillanic acid (VII), 6 - (3 - methyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl)carbonamido - penicillanic acid (VIII), 6 - (3 - *p* - tolyl - 6-methyl - 3,4 - dihydroquinazolin - 2 - yl)carbonamido - penicillanic acid (IX), 6 - (1 - *p* - methoxybenzyl - benzimidazol - 2 - yl)carbonamido - penicillanic acid (X), 7 - (1 - vinyl - imidazol - 2 - yl)carbonamido - cephalosporanic acid (XI) and 7 - (1 - phenyl - 5 - methoxy - benzimidazol - 2 - yl)carbonamido - desacetoxy-cephalosporanic acid (XII), the numbers following each compound indicating the relevant Example, and their alkali metal, alkaline earth metal and amine salts.

The antibiotic activity against gram-positive and gram negative microorganisms of most of these compounds can be seen from the results obtained in the following agar serial dilution test:

A stock solution of the compound at 2,000 μg/ml. is prepared in a sterile suitable vehicle. Two fold dilutions are made with sterile 1/20 Mol. phosphate buffer pH 6.5 (KH_2PO_4—NaOH). 1 ml. quantities of each dilution are incorporated in 19 ml. brain-heart infusion agar in sterile Petri dishes. The hardened surface is inoculated with test organisms and incubated for 24 hours at 37° C. The minimal inhibitory concentration of the compound (MIC), i.e. the least amount of antibiotic that completely inhibits the test organism, is expressed in μg./ml. The MIC values of the compounds identified by the Example number are shown in the following Table.

Microorganism	MIC values in ug./ml. Compound of Example									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Gram-positive										
Bacillus subtilis 6633	0.5	>100	0.12	6	6	0.5	6	3	1.5	0.5
Staphylococcus aureus A55	1	>100	0.12	3	6	3	12.5	12.5	12.5	1.5
A321	0.5	1.8	0.12	3	50	3	12.5	12.5	6	0.5
A355')	6	>100	6	12.5	50	6	50	50	50	3
L160a')	6	1.5	3	6	50	6	25	25	25	1.5
Streptococcus haemolyticus A266	1	0.15	0.06	1	3	1.5	1.5	0.25	1	0.25
Streptococcus faecalis L80	12.5	3	1.5	6	>100	12.5	50	25	>100	1.5
Diplococcus pneumoniae L54	3	9	1	1.5	25	3	3	>100	1.5	0.25
Gram-negative										
Brucella melitensis A488	6	>100	3	>100	>100	25	50	>100	100	25
Pasteurella multicida A723	6	3	6	50	>100	12.5	25	25	100	50
Shigella equirulis T3	12.5	25	25	50	100	100	>100	100	100	25

') penicillinase forming microorganism.

The penicillanic and cephalosporanic acid derivatives conforming to general formulae (I) and (II) are preferably employed for therapeutic purposes, when appropriate, in the form of a non-toxic alkali metal or alkaline earth metal salt such as the sodium, potassium or calcium salt. Other salts that may be used in pharmaceutical preparations include the non-toxic suitability crystallising salts with organic amine bases such as, for example, trialkylamines, pricaine and dibenzylamine.

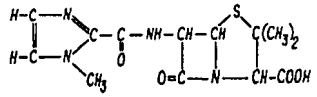
When used for therapeutic purposes the compounds of general formulae (I) and (II) may be used as such or in the form of a pharmaceutical preparation customarily employed for the administration of therapeutically active substances, especially antibiotics. The invention includes within its scope pharmaceutical preparations comprising, as the active ingredient, at least one of the novel penicillanic or cephalosporanic acid derivatives of general formulae (I) or (II), or a non-toxic alkali metal, alkaline earth metal, or amine salt thereof, in association with a pharmaceutically acceptable carrier. The preferred types of pharmaceutical preparations are those suitable for oral administration and especially capsules. Such capsules are preferably made of absorbable material, such as gelatin, and may contain the active substance alone or in admixture with a solid or liquid diluent. They may also contain the active substance attached to or incorporated in a carrier substance in such a way that the active substance is released over an extended period of time after ingestion. Liquid preparations may be in the form of solutions suitable for parenteral administration.

By the term "methods known *per se*" as used in this specification is meant methods hitherto used or described in the chemical literature.

The following Examples illustrate the preparation of compounds of the invention.

EXAMPLE I.

Preparation of 6 - (1 - methyl - imidazol - 2 - yl)carbonamido - penicillanic acid.



The reaction was carried out in a three-necked vessel provided with a thermometer, a gas inlet tube through which nitrogen was introduced continuously and a dropping funnel on top of which was placed a gas outlet tube filled with a desiccant. Stirring by magnetic means was employed.

A solution of 0.79 ml. (10 mmol) of 1-methyl-imidazole in 15 ml. of dry toluene was cooled to −60° C. by means of external cooling, and a solution of 10 mmol of n-butyllithium and 1.5 ml. (10 mmol) of N,N,N′,N′-tetramethylethylenediamine in 4.3 ml. of hexane and 10 ml. of dry petroleum ether was added drop-wise at a rate adjusted so that the internal temperature of the reaction mixture did not go higher than −60° C. After two hours additional stirring at −60° C., a solution of 2.5 g. (7 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid in 10 ml. of dry toluene was introduced drop-wise at −60° C., followed by 60 minutes additional stirring at −60° C. The reaction mixture was poured into a well stirred mixture of 50 ml. of ice-water and 25 ml. of ethyl acetate, while simultaneously dilute hydrochloric acid was added in order to keep the pH below 7. By means of the addition of dilute sodium hydroxide solution the pH was brought from 4.0 to 7.0. After separation of the layers, the organic layer was discarded and the aqueous layer acidified to pH 3.0. Next, the aqueous layer was extracted three times with 25 ml. of diethyl ether and finally once with a mixture of 50 ml. of diethyl ether and 5 ml. of ethyl acetate. The extracts were combined, washed three times with a small volume of ice-water, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure, and dried *in vacuo*. The obtained, somewhat yellow, solid weighed 570 mg. Yield 25%.

According to thin-layer chromatography the product was contaminated with only very slight amounts of sulphur containing by-products, while the PMR spectrum indicated the presence of residual traces of solvents.

Analysis of the PMR spectrum of the final product dissolved in hexadeuteroacetone (60 Mc, δ-values in ppm, internal reference:tetramethylsilane):

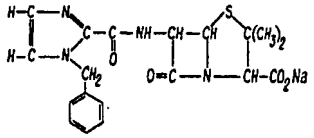
C_3–CH_3	:	1.54 and 1.64 (6 protons)
N–CH_3	:	3.96 (3 protons)
C_2–H	:	4.38 (1 proton)
C_5–H and C_6–H	:	5.45 → 5.85 (sharp multiplet, 2 protons)
$C_{4'}$–H and $C_{5'}$–H	:	6.91 and 7.17 (two slightly broadened singlets, 2 protons)
N–H	:	about 8.05 (broadened doublet, J≈8 cps, about 1 proton)
COOH and H_2O	:	about 8.5

Partial analysis of the IR spectrum of the final product dissolved in chloroform (values in cm^{-1})

about 3500	OH
3485	NH
1788	C=O β-lactam
1722	C=O carboxyl
1679	C=O amide
about 1525	probably N–H bending and/or C=N imidazole
1492 and 1468	C=N and/or C=C imidazole

EXAMPLE II.

Preparation of 6 - (1 - benzyl - imidazol - 2 - yl)carbonamido - penicillanic acid, sodium salt.



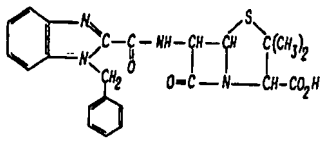
In the same way as described in Example I 10 mmol of 1-benzyl-imidazole suspended in toluene was treated with 10 mmol of the n-butyl lithium: tetramethylene-ethylenediamine complex, followed by the introduction of 7 mmol of the trimethylsilyl ester of 6-isocyanato-penicillanic acid dissolved in toluene. In the isolation procedure the penicillin was extracted from the aqueous layer, acidified to pH5, by means of diethyl ether. To this extract was finally added a solution of sodium α-ethyl capronate dissolved in diethyl ether. The obtained slightly yellowish sodium salt weighed 600 mg.

Thin-layer chromatograms of the final product showed only one spot belonging to a sulphur containing compound. The alleged structure was confirmed by the IR and PMR spectra, which revealed the presence of a small amount of sodium α-ethylcapronate as impurity in the final product. Analysis of the PMR spectrum of the final product dissolved in a mixture of hexadeutero-acetone and a small amount of D_2O (60 Mc, δ-values in ppm, internal reference: tetramethylsilane):

C_3–CH_3	:	1.62 and 1.64 (6 protons)	
C_2–H	:	4.30 (1 proton)	
N–CH_2	:	about 5.7 (broadened singlet	4 protons
C_5–H and C_6–H	:	5.6 → 5.85 (AB–quartet)	
$C_{5'}$–H or $C_{4'}$–H	:	approximately 7.01 (sharp doublet, J = 1 cps, 1 proton)	
C_6H_5	:	about 7.25	6 protons
$C_{4'}$–H or $C_{5'}$–H	:	approximately 7.31 (sharp doublet, J = 1 cps)	
N–H (partially N–D)	:	about 8.2 (broadened doublet, about 0.4 proton)	

EXAMPLE III.

Preparation of 6 - (1 - benzyl - benzimidazol - 2 - yl) carbonamido - penicillanic acid.



To a solution of 8.32 g. (40 mmol) of 1-benzyl-benzimidazole in 80 ml. of anhydrous tetrahydrofuran, cooled to −65° C., was added drop-wise 17.2 ml. of a solution of n-butyllithium (about 40 mmol) in hexane at a rate adjusted to maintain internal temperatures just below −60° C. After two hours additional stirring at −60° C., a solution of 10.0 g. (31.8 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid in 40 ml. of anhydrous toluene was introduced drop-wise again at internal temperatures just below −60° C. After two hours additional stirring at −60° C., the reaction mixture was poured into a well stirred mixture of 200 ml. of ice-water and 100 ml. of ethyl acetate with simultaneous addition of dilute hydrochloric acid in order to keep the pH approximately at 3. After a constant pH of 3.0 had been attained, the mixture was neutralized to pH 7 by means of dilute sodium hydroxide solution, and the layers were separated. The organic layer was discarded and the aqueous layer was acidified with dilute hydrochloric acid to pH 4.0, followed by repeated extractions with diethyl ether. The extracts, practically equally pure solutions of the desired penicillin, were combined, washed three times with a small volume of ice-water, dried over anhydrous magnesium sulphate filtered and evaporated to dryness *in vacuo*.

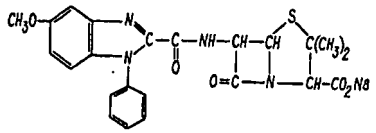
According to thin-layer chromatography and a PMR spectrum the crude product obtained in this manner, an amorphous yellow coloured solid, was already in a reasonably pure state except for a copious amount of tightly adherent diethyl ether. In order to obtain pure crystalline material, the solid was dissolved in 50 ml. of chloroform. This solution was seeded with a few crystals obtained through column chromatography (silica, diethyl ether) of crude product prepared in another run in which the organo-metallic reagent had been prepared by means of the butyllithium: tetramethylethylenediamine complex. The seeded solution kept overnight at 30° C. yielded a white crystalline deposit, which was separated by suction filtration, washed with cold chloroform and cold acetone, and dried to constant weight *in vacuo* (yield 1.5 g.). The final product was of high purity, according to thin-layer chromatography and its PMR and IR spectra, and preserved its quality on storage.

Analysis of the PMR spectrum of the final product dissolved in hexadeutero-acetone and a small amount of hexadeutero-dimethylsulphoxide (60 Mc, δ-values in ppm, internal reference: tetramethylsilane):

C_3–CH_3		1.60 and 1.71 (6 protons)	
C_2–H		4.46 (1 proton)	
C_5–H and C_6–H	:	5.67 → 5.99 (sharp sextet, J_{AB} = 4.2, $J' \approx 9$ cps	4 protons
N–CH_2	:	6.02 (slightly broadened singlet)	
C_6H_5	:	7.25 (centre of relatively sharp signal)	9 protons
benzo C_6H_4	:	7.2 → 7.95 (sharp multiplet)	
COOH	:	8.10 (sharp singlet, about 1 proton)	
N–H	:	8.63 (relatively sharp doublet, $J \approx 9$ cps, about 1 proton)	

EXAMPLE IV.

Preparation of 6 - (1 - phenyl - 5 - methoxy - benzimidazol - 2 - yl)carbonamido-penicillanic acid, sodium salt.



A suspension of 2.24 g. (10 mmol) of 1-phenyl-5-methoxy-benzimidazole in 10 ml. of dry toluene was cooled to 70° C., then treated with a solution of 10 mmol of n-butyllithium and 10 mmol of N,N,N',N'-tetramethylethylenediamine in 4.3 ml. of hexane and 10 ml. of petroleum ether at temperatures below −60° C., followed by 2 hours additional stirring at −60° C. Subsequently a solution of 2.5 g. (7 mmol) of the trimethylsilyl ester of 6-isocyanatopenicillanic acid in 10 ml. of dry toluene was added slowly to the well stirred suspension at −60° C. After additional stirring for one hour at −60° C., the reaction mixture was poured into a well stirred, acidified mixture of 50 ml. of ice-water and 25 ml. of ethyl acetate with the simultaneous addition of dilute hydrochloric acid in order to keep the pH below 7. After reaching a constant pH 3, the pH was raised to 7 by means of dilute sodium hydroxide solution, and the layers were separated. The organic layer was discarded. The main portion of the amount of the desired penicillin present in the aqueous layer was removed by three extractions with 50 ml. of diethyl ether at pH 4.5. The extracts were combined, washed three times with a small volume of ice-water, dried over anhydrous magnesium sulphate, filtered and concentrated to some extent *in vacuo*. To this solution was added a solution of sodium α-ethylcapronate, which resulted in the precipitation of an almost white solid product. The salt was collected by filtration, washed three times with diethyl ether and dried *in vacuo* to constant weight. Yield: 1.50 g.

According to thin-layer chromatography the salt consisted of one main component and a by-product or a degradation product. According to a PMR spectrum of the salt it consisted of about 70% of the desired penicillin, about 15% of presumably a degradation product and some sodium α-ethylcapronate and some sodium acetate.

Analysis of the PMR spectrum of the sodium salt of 6-(1-phenyl-5-methoxy-benzimidazol - 2 - yl)carbonamido - penicillanic acid dissolved in a 1:1 mixture of hexadeutero-actone and hexadeutero-dimethylsulphoxide (60 Mc, δ-values in ppm, internal reference:tetramethylsilane):

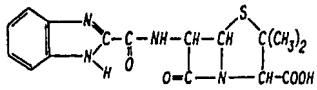
C_1-CH_3		1 64 and 1.69 (6 protons)
$C-CH_3$		3.86 (3 protons)
C_2-H	:	4.40 (1 proton)
C_5-H and C_6-H	:	5.45 → 5.80 (multiplet, 2 protons)
$C_{4'}-H$, $C_{6'}-H$ and $C_{7'}-H$	:	6.85 → 7.35 (multiplet, 3 protons)
$N-C_6H_5$	:	about 7.45 (5 protons)
N–H	:	about 8.4 (broadened doublet, $J \approx 8$ cps, less than 1 proton)

Partial analysis of the IR spectrum of the product (KBr-disk, values in cm^{-1})

3400	:	NH
2838	:	possibly methoxy
1765	:	C=O β-lactam
1690	:	C=O amide
± 1610	:	C=O carboxylate + C=C aromatic
1515	:	NH def. + possibly C=N
1498	:	C=C aromatic
758 and 689	:	aromatic substitution pattern

EXAMPLE V.

Preparation of 6 - (benzimidazol - 2 - yl)carbonamido - penicillanic acid.



Experiment 1

To a suspension of 2.14 g. (18 mmol) of benzimidazole in 65 ml. of dry dichloromethane was added 3.8 ml. (27 mmol) of triethylamine, followed by the drop-wise introduction of 3.4 ml. (23.5 mmol) of redistilled trimethylchlorosilane in a nitrogen atomosphere. After subsidence of the exothermic reaction, the reaction mixture was diluted with 65 ml. of anhydrous toluene. By concentration *in vacuo* the volume was reduced to about 35 ml., followed by a filtration under nitrogen. By means of a PMR spectrum it was checked that the final clear solution in toluene contained approximately 16 mmol of 1-trimethylsilyl-benzimidazole. This solution was cooled to −60° C., followed by the drop-wise introduction of a mixture of 16 mmol of n-butyllithium and 16 mmol of N,N,N',N'-tetramethylethylenediamine dissolved in a mixture of 7 ml. of hexane and 16 ml. of dry petroleum ether at a rate adjusted so that the internal temperatures did not go higher than −60° C. After one hour additional stirring at −60° C., a solution of 4.0 g. (12.7 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid in 20 ml. of dry toluene was introduced drop-wise at temperatures just below −60° C., followed by 1 hours additional stirring at −60° C. While simultaneously adding dilute hydrochloric acid in order to keep the pH below 7, the reaction mixture was slowly poured into a well stirred mixture of 100 ml. of ice-water and 75 ml. of ethyl acetate. After reaching a constant pH 3, the pH was raised to 7 by means of dilute sodium hydroxide solution, and the layers separated. The organic layer was discarded. The aqueous layer was brought to pH

4.0, and twice extracted with 50 ml. of diethyl ether and once with 50 ml. of a 1:1 mixture of ethyl acetate and diethyl ether. The extracts were combined, washed three times with a small volume of ice-water, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to small volume. To this solution was added a solution of sodium α-ethylcapronate, which resulted in the precipitation of a slightly yellowish solid product. The product was collected by filtration, washed three times with diethyl ether and dried *in vacuo* to constant weight. Yield 400 mg. Its purity was estimated to be about 75%. Its IR spectrum was in accordance with the alleged structure.

Experiment 2

A solution of 10 mmol of 1-trimethylsilyl-benzimidazole in 10 ml. of toluene (prepared as described above) was evaporated *in vacuo* to dryness. The residue was taken up in 20 ml. of anhydrous tetrahydrofuran (distilled from lithium aluminium hydride). To this clear solution cooled to $-70°$ C. was added drop-wise a solution of 10 mmol of n-butyllithium in 4.3 ml. of hexane, the temperature not being allowed to rise above $-60°$ C. After 2 hours additional stirring at $-60°$ C., a solution of 2.5 g. (7 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid in 10 ml. of toluene was added drop-wise, the temperature being kept below $-60°$ C. After additional stirring for 1 hour the reaction mixture was treated as described above except that the extraction of the acidified aqueous layer was carried out with diethyl ether only. The ether extract was completely evaporated, the resulting slightly yellowish solid stirred with 10 ml. of petroleum ether, collected by filtration and dried to constant weight. Yield 1.1 g. (about 40%).

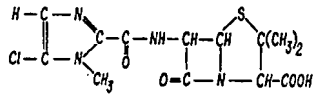
According to thin-layer chromatography and a PMR spectrum the purity of the product was about 85%, the impurities for the main part consisting of residual solvents.

Analysis of the PMR spectrum of 6-(benzimidazol-2-yl)carbonamido-penicillanic acid dissolved in hexadeutero-dimethylsulphoxide (60 Mc, δ-values in ppm, internal reference: tetramethylsilane):

C_3–CH_3	:	1.60 and 1.71 (6 protons)
C_2–H	:	4.49 (1 proton)
C_5–H and C_6–H	:	5.45 → 6.0 (multiplet, 2 protons)
C_6H_4	:	7.15 → 7.85 (multiplet, 4 protons)
$(N–H)_2$, COOH and H_2O	:	7.2 → 8.9 with sharp N–H doublet at 8.62, J≈8.5 cps (more than 3 protons)

EXAMPLE VI.

Preparation of 6 - (5 - chloro - 1 - methyl - imidazol - 2 - yl)carbonamido - penicillanic acid.



To a solution of 0.544 g. (4.67 mmol) of 5-chloro-1-methyl-imidazol in 10 ml. of dry toluene was added between $-60°$ and $-70°$ C. a solution of approximately 4.67 mmol of n-butyllithium and 0.7 ml. (4.67 mmol) of N,N,N',N' - tetramethyl-ethylenediamine dissolved in 2.0 ml. of hexane and 10 ml. of petroleum ether. The resulting solution was additionally stirred for 15 minutes at $-60°$ C. and then a solution of 1.4 g. 4.43 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid dissolved in 5 ml. of toluene at $-60°$ C. was added drop-wise. After additional stirring for 1 hour at $-60°$ C., the reaction mixture was worked up in the usual way. The penicillin was extracted from the aqueous layer acidified to pH 4 with two 50 ml. portions of diethyl ether. The quite pure extract, according to thin-layer chromatography, was washed twice with a small amount of ice-water, dried over anhydrous

magnesium sulphate, filtered and completely evaporated at reduced pressure. Yield 300 mg. off a slightly yellowish solid.

According to thin-layer chromatography the final product was practically pure with respect to sulphur containing by-products. The product responded strongly positive to qualitative chlorine tests. Its alleged structure was confirmed by its IR spectrum and its PMR spectrum (absence of an imidazole C_2—H absorption).

Analysis of the PMR spectrum of the final product dissolved in hexadeutero-acetone (60 Mc, δ-values in ppm, internal reference:tetramethylsilane):

C_3–CH_3	:	1.59 and 1.69 (6 protons)	
N–CH_3	:	3.97 (3 protons)	
C_2–H	:	4.45 (1 proton)	
C_5–H	:	5.63 and 5.70 (J_{AB} = 4.2 cps)	2 protons
C_6–H	:	5.70, 5.77, 5.84 and 5.91 (J_{AB} = 4.2 cps $J' \approx 8.5$ cps)	2 protons
$C_{4'}$–H	:	7.01 (1 proton)	
COOH (+H_2O)[a]	:	about 7.5 (more than 1 proton)	
N–H[b]	:	about 7.95 and 8.1 ($J' \approx 8.5$ cps, about 1 proton)	

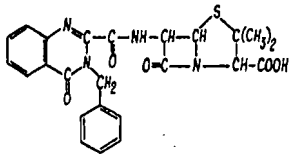
a: Shifts to high field upon addition of a small amount of D_2O

b: Disappears upon addition of a small amount of D_2O

The PMR spectrum of 5-chloro-1-methyl-imidazole in the same solvent showed three absorptions: N–CH_3 at 3.62, C_4–H at 6.82 and C_2–H at 7.52 ppm.

EXAMPLE VII.

Preparation of 6 - (3 - benzyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl)carbon-amido penicillanic acid.



To a suspension of 2.22 g. (9.4 mmol) of 3-benzyl-4-oxo-3,4-dihydro quinazoline in 25 ml. of dry tetrahydrofuran was added drop-wise a solution of approximately 9.4 mmol of n-butyllithium in 4 ml of hexane at −70° C, and the mixture was additionally stirred for two hours at temperatures between −60° C and −70° C. Next, a solution of 2.48 g (7.9 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid in 25 ml of dry toluene was introduced drop-wise at −60° to −70° C, followed by one hours additional stirring at the same temperature. The reaction mixture was treated in the usual way. Finally, the desired penicillin was extracted with diethyl ether from the aqueous layer acidified to pH 5.0. The extract was as usual washed with a small amount of cold water, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness *in vacuo*. The solid residue was washed with diethyl ether and light petroleum ether. The final dry product weighed 1.12 g.

According to thin-layer chromatography and the PMR spectrum the purity of the final product was about 80%; the impurities consisted mainly of residual petroleum ether and acetic acid and a small amount of a degradation product. The alleged structure of the final product was confirmed by IR and PMR spectra. However,

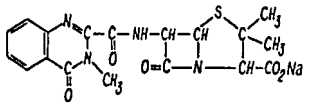
according to thin-layer chromatography and spectroscopic investigations this penicillin possibly displays tautomerism involving the side chain amide bond, which may reside partly in the hydroxy-imino form.

Partial analysis of the IR spectrum of the final product (KBr-disk, values in cm^{-1}).

± 3400 ± 3420	NH from $\overset{O}{\overset{\|\|}{C}}-NH$ and OH presumably from $\overset{OH}{\overset{\|}{C}}=N$
3090 3065 3035	$=C-H$
1788	$C=O$ β-lactam
1735	$C=O$ carboxyl
± 1640 → ± broad 1690, intensive area, covering at least two intensive absorptions	
1600	$C=C$ aromatic
752 690	aromatic substitution pattern

EXAMPLE VIII.

Preparation of 6 - (3 - methyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl)carbonamido-penicillanic acid, sodium salt.



In the same way as described in Example VII, a suspension of 1.60 g (10 mmol) of 3 - methyl - 4 - oxo - 3,4 - dihydro - quinazoline in tetrahydrofuran was treated with 10 mmol of n-butyllithium dissolved in hexane, followed by the introduction of 7.9 mmol of the trimethylsilylester of 6-isocyanato-penicillanic acid dissolved in toluene. In the isolation procedure the penicillin was extracted from the aqueous layer with diethyl ether at pH 4.0. To this extract was finally added a solution of sodium α-ethylcapronate dissolved in ethyl acetate. The obtained solid sodium salt weighed 630 mg.

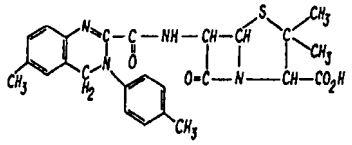
According to PMR spectra and thin-layer chromatograms, the final product was about 80% pure and was mainly contaminated with sodium α-ethylcapronate and sodium acetate. According to thin-layer chromatography and spectroscopic investigations this penicillin too probably shows tautomerism involving the side chain amide bond.

Analysis of the PMR spectrum of the final product dissolved in hexadeuterodimethylsulphoxide containing a small amount of D_2O(60 Mc, δ-values in ppm, internal reference:tetramethylsilane):

C_3–CH_3	about 1.6 (broadened singlet, 6 protons)
N–CH_3	3.06 (somewhat broadened singlet, 3 protons)
C_2–H	4.11 and 4.15 (approximately 1:1 ratio, 1 proton)
C_5–H and C_6–H	5.2 → 5.6 (multiplet, 2 protons)
C_6H_4 and N–H	7.0 → 7.9 (multiplet, between 4 and 5 protons)

EXAMPLE IX.

Preparation of 6 - (3 - *p* - tolyl - 6 - methyl - 3,4 - dihydroquinazolin - 2 - yl)-carbonamido-penicillanic acid.

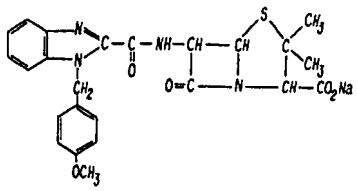


In the same way as described in preceding Examples, 2.24 g. (9.5 mmol) of 3 - *p* - tolyl - 6 - methyl - 3,4 - dihydroquinazoline dissolved in 25 ml of tetrahydrofuran was treated at −70° C with approximately 9.5 mmol of n-butyl-lithium dissolved in hexane, followed by the addition of 2.50 g. (7.96 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid dissolved in 10 ml of toluene.

According to thin-layer chromatography the reaction product contained two sulphur containing compounds, the desired penicillin and a minor amount of another compound. In the isolation procedure the desired penicillin was incompletely but in almost pure state extracted from the aqueous layer, acidified to pH 5.5, by means of diethyl ether. The combined extracts were washed with ice-water, dried over anhydrous magnesium sulphate, filtered and evaporated to dryness *in vacuo*. The obtained solid product weighed 1.26 g. The alleged structure was confirmed by IR and PMR spectra of the final product.

EXAMPLE X.

Preparation of 6 - (1 - *p* - methoxybenzyl - benzimidazol - 2 - yl)carbonamido-penicillanic acid, sodium salt.

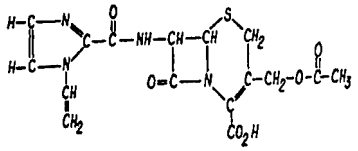


In the same way as described in preceding Examples, 2.22 g. (9.3 mmol) of 1 - *p* - methoxybenzyl - benzimidazole dissolved in 25 ml of tetrahydrofuran was treated with approximately 9.3 mmol of n-butyllithium dissolved in hexane at −60° to −70° C, followed by the drop-wise introduction of 2.5 g (7.96 mmol) of the trimethylsilyl ester of 6-isocyanato-penicillanic acid dissolved in 10 ml of toluene. In the isolation procedure the desired penicillin was incompletely extracted from the aqueous layer acidified to pH 5.2 with diethyl ether. The combined extracts was washed with ice-water, dried over anhydrous magnesium sulphate, filtered and finally treated with a solution of sodium α-ethylcapronate dissolved in a 9:1 mixture of diethyl ether and ethyl acetate. The obtained sodium salt weighed 800 mg. Partial analysis of the IR spectrum of the product (KBr-disk, value in cm^{-1}).

about 3375	:	NH
2840	:	C–H of OCH_3
1770	:	C = O β-lactam
1685	:	C = O amide
± 1610	:	C = O carboxylate + C = C aromatic
1510	:	N – H def. + C = C aromatic
735	:	aromatic substitution pattern

EXAMPLE XI.

Preparation of 7 - (1 - vinyl - imidazol - 2 - yl)carbonamido - cephalosporanic acid.



To a solution of 940 mg (10 mmol) of 1-vinyl-imidazole in 25 ml of dry tetrahydrofuran was added drop-wise at −70° C a solution of approximately 10 mmol of n-butyllithium in 4.3 ml of hexane, followed by 30 minutes additional stirring at −60° to −70° C. Employing the inverse addition method, this solution was added drop-wise at −60° to −70° C to a solution of 8 mmol of the trimethylsilyl ester of 7-isocyanato-cephalosporanic acid in 20 ml of toluene, followed by 90 minutes additional stirring at approximately −65° C. The reaction product was treated in the usual way. The desired cephalosporin was incompletely extracted from the aqueous layer, acidified to pH 3.5 by means of ethyl acetate. The extract was washed with ice-water, dried over magnesium sulphate, filtered and completely evaporated. The residue was digested with 25 ml of dry diethyl ether. The resulting solid was collected by filtration, washed with diethyl ether and dried *in vacuo*. Yield 810 mg. The purity of the product was about 80%. In order to facilitate identification of the product by spectroscopic methods, 600 mg of the product were purified by column chromatography. In this way 390 mg of almost pure, dry product were obtained. Partial analysis of the PMR spectrum of 7-(1-vinyl-imidazol-2-yl)-carbonamido-cephalosporanic acid dissolved in hexadeutero-dimethyl-sulphoxide (60 Mc, δ values in ppm, internal reference: tetramethylsilane):

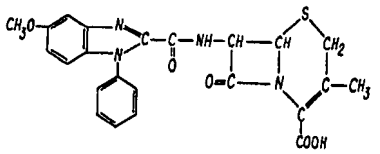
CH_3	2.04 (3 protons)
$S-CH_2$	± 3.57 (centre of broadened absorptions, 2 protons)
$O-CH_2$, C_6-H, C_7-H and $=CH_2$	4.55 → 6.0 (superimposing multiplets, 6 protons)
$C_{5'}-H$ or $C_{4'}-H$:7.13	(narrow doublet, 1 proton)
$C_{4'}-H$ or $C_{5'}-H$:7.89	(narrow doublet) } 2 protons
$N-CH=$	7.74 → 8.13 (quartet; $J_1 \approx 15$ cps, $J_2 \approx 9$ cps) } 2 protons
$N-H$	8.86 (relatively sharp doublet, $J \approx 8.5$, cps, 1 proton)

Partial analysis of the IR spectrum of the product (KBr-disk, values in cm^{-1}):

3390	N–H
about 2500	OH dimer
1780	C = O β-lactam
1730	C = O ester
1550–1520	N–H def.
1250–1220	C–O–C acetate

EXAMPLE XII.

Preparation of 7 - (1 - phenyl - 5 - methoxy - benzimidazol - 2 - yl)carbonamido-desacetoxycephalosporanic acid.



Exactly as described in Example IV, 2.24 g. (10 mmol) of 1-phenyl-5-methoxy-benzimidazole were reacted with 10 mmol of n-butyllithium in the presence of 10 mmol of N,N,N′,N′-tetramethylethylenediamine, followed by the addition of a solution of 2.45 g (8 mmol) of the trimethylsilyl ester of 7-isocyanato-desacetoxycephalosporanic acid in a mixture of 4 ml of toluene and 5 ml of tetrahydrofuran. The reaction mixture was poured into a well stirred, acidified mixture of 50 ml of ice-water and 25 ml of ethyl acetate with simultaneous addition of dilute hydrochloric acid. The pH of the mixture was subsequently raised to 7, and the layers were separated. The aqueous layer was extracted twice with diethyl ether. Thin-layer chromatography was applied on the combined organic layer and the aqueous layer and this indicated the presence of a substantial amount of 1 - phenyl - 5 - methoxy-benzimidazole in the former layer and of N,N′ - di - desacetoxycephalosporanyl - urea in the latter layer, in addition to the desired product and relatively small amounts of degradation product(s) and (presumably) n - butyl - desacetoxycephalosporin. The major by-products suggested that the low-temperature conditions for the reaction with this isocyanate were somewhat too mild for completion of the conversion.

The desired product was incompletely removed from the aqueous layer by means of four extractions with 50 ml of ethyl acetate at pH 6.5, 6.0, 5.0 and 4.5 respectively. These extracts were combined, washed with ice-water, dried over anhydrous magnesium sulphate, filtered, stirred with charcoal, filtered and concentrated *in vacuo* to a volume of approximately 25 ml, when spontaneous crystallisation took

place. The crystals were filtered off by suction filtration, washed repeatedly with cold diethyl ether and dried *in vacuo* to constant weight. Yield 900 mg. According to thin-layer chromatograms and IR and PMR spectra the final product was of high purity.

Analysis of the PMR spectrum of the final product dissolved in hexadeutero-dimethylsulphoxide (60 Mc, δ values in ppm, internal reference 2,2-dimethyl-silapentane-5-sulphonate):

CH_3	2.10 (3 protons)
$S-CH_2$	3.5 (broadened singulet, 2 protons)
$O-CH_3$	3,85 (3 protons)
C_6-H	5.07 and 5.15 (J_{AB} = 4.7 ± 0.2 cps, 1 proton)
C_7-H	5.56, 5.62, 5.69 and 5.77 (J_{AB} = 4.7, J≈8.7 cps, 1 proton)
$C_{6'}-H$ and $C_{7'}-H$	7.05 (broadened singulet, 2 protons)
$C_{4'}-H$	7.35 (broadened singulet, 1 proton)
$N-C_6H_5$	7.5 (5 protons)
N–H	9.23 and 9.37 (sharp doublet, J = 8.7 ± 0.2 cps, about 0.7 proton)

Elementary analysis for $C_{23}H_{20}N_4O_5S$

	Found	Calculated
C	59.23 %	59.47 %
H	4.64 %	4.35 %
N	12.23 %	12.06 %
S	6.78 %	6.90 %
(O)	17.12 %	17.22 %

The petroluem ether mentioned in the foregoing Examples has a boiling point of 40—60° C.

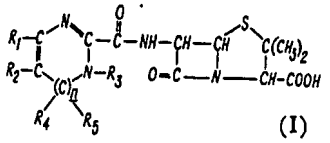
The following Example illustrates a pharmaceutical composition according to the invention.

EXAMPLE XIII.

A quantity of 100 to 2000 mg. of 6 - (1 - benzyl - benzimidazol - 2 - yl)-carbonamido-penicillanic acid is aseptically introduced into a vial suitable for injectable compositions. Before use the powder is dissolved in a suitable amount of sterile and pyrogen-free water.

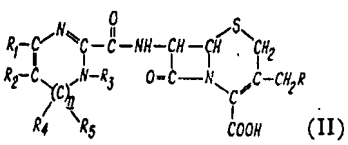
WHAT WE CLAIM IS:—

1. Compounds of the general formulae:



(I)

and



(II)

(wherein R represents a hydrogen atom, a hydroxy group or a lower alkanoyloxy group, or the grouping —CH_2R and the carboxy group in formula (II) are linked together to form a lactone group, R_1 and R_2 are the same or different and each represents a hydrogen atom, a lower alkyl or lower alkoxy group, a cycloalkyl group of 5 to 8 carbon atoms, a phenyl or phenoxy group, or a chlorine or fluorine atom, or R_1 and R_2 and the carbon atoms to which they are attached collectively form a phenyl group or a cycloalkylene group with at least one double bond therein, the phenyl or cycloalkylene group optionally carrying one or more substituents preferably selected from the chlorine atom and lower alkyl and lower alkoxy groups, R_3 represents a hydrogen atom, a lower alkyl, vinyl or allyl group, a cycloalkyl group of 5 to 8 carbon atoms, a phenyl(lower)alkyl or phenyl group optionally carrying one or more substituents on the ring selected from lower alkyl and lower alkoxy groups and the chlorine atom, R_4 and R_5 are the same or different and each represents a hydrogen atom or a lower alkyl group, or R_4 and R_5 together represent a keto oxygen atom, and n is zero or 1) and alkalimetal, alkaline earth metal and amine salts thereof.

2. Compounds according to claim 1 wherein R_1 and R_2 each represent a hydrogen atom, a methyl, ethyl, propyl or butyl group, a methoxy, ethoxy, propoxy or butoxy group, a cyclopentyl, cyclohexyl or cycloheptyl group, a phenyl or phenoxy group, or a chlorine or fluorine atom, or R_1 and R_2 and the carbon atoms to which they are attached collectively form a phenyl group or a cyclohexenylene group, the phenyl or cyclohexenylene group optionally carrying one or more substituents selected from the chlorine atom and methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy and butoxy groups, R_3 represents a hydrogen atom, a methyl, ethyl, propyl or butyl group, a vinyl or allyl group, a cyclopentyl, cyclohexyl or cycloheptyl group, a benzyl or phenyl group optionally carrying one or more substituents on the ring selected from methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy and butoxy groups and the chlorine atom, R_4 and R_5 each represent a hydrogen atom or a methyl, ethyl, propyl or butyl group, or R_4 and R_5 together represent a keto oxygen atom, and R and n, are as defined in claim 1, and alkali metal, alkaline earth metal and amine salts thereof.

3. Compounds according to claim 1 wherein R_1 and R_2 both represent hydrogen atoms or one represents a hydrogen atom and the other a chlorine atom, or R_1 and R_2 and the carbon atoms to which they are attached form a phenyl group unsubstituted or substituted by a lower alkyl group, R_3 represents a hydrogen atom, a lower alkyl or vinyl group, or a phenyl or benzyl group unsubstituted or carrying on the phenyl ring a lower alkyl or lower alkoxy group, and R, R_4, R_5 and n are as defined in claim 1, and alkali metal, alkaline earth metal and amine salts thereof.

4. Compounds according to claim 3 wherein the lower alkyl groups are methyl or ethyl and the lower alkoxy groups are methoxy or ethoxy.

5. Compounds according to claim 3 or 4 wherein R_4 and R_5 each represent a hydrogen atom or R_4 and R_5 together represent a keto oxygen atom, and n is 1, and alkali metal, alkaline earth metal and amine salts thereof.

6. 6 - (1 - Methyl -imidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

7. 6 - (1 - Benzyl - imidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

8. 6 - (1 - Benzyl - benzimidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

9. 6 - (1 - Phenyl - 5 - methoxy - benzimidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

10. 6 - (Benzimidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

11. 6 - (5 - Chloro - 1 - methyl - imidazol - 2 - yl)carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

12. 6 - (3 - Benzyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl)carbonamido-penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

13. 6 - (3 - Methyl - 4 - oxo - 3,4 - dihydroquinazolin - 2 - yl)carbonamido-penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

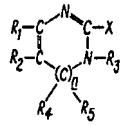
14. 6 - 3 - *p* - Tolyl - 6 - methyl - 3,4 - dihydroquinazolin - 2 - yl) - carbonamido - penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

15. 6 - (1 - *p* - Methoxybenzyl - benzimidazol - 2 - yl)carbonamido-penicillanic acid and alkali metal, alkaline earth metal and amine salts thereof.

16. 7 - (1 - Vinyl - imidazol - 2 - yl carbonamido - cephalosporanic acid and alkali metal, alkaline earth metal and amine salts thereof.

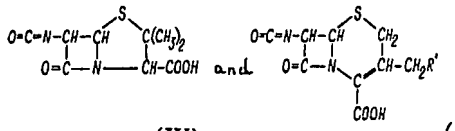
17. 7 - (1 - Phenyl - 5 - methoxy - benzimidazol - 2 - yl)carbonamido-desacetoxycephalosporanic acid and alkali metal, alkaline earth metal and amine salts thereof.

18. Process for the preparation of compounds of the general formulae specified in claim 1, and alkali metal, alkaline earth metal and amine salts thereof, which comprises reacting a heterocyclic compound of the general formula:



(III)

(wherein R_1, R_2, R_3, R_4, R_5 and n are as defined in claim 1 and X represents a lithium atom or a magnesium chloride or magnesium bromide group) with an ester of 6-isocyanatopenicillanic acid or an ester or lactone derivative of a 7-isocyanato-cephalosporanic acid, the two acids having the formulae:



(IV) (V)

respectively (wherein R' is a hydrogen atom, a lower alkanoyloxy group or a protected hydroxy group) and hydrolysing the resulting organo-metal intermediate product to remove the metal ion and, when present, the esterifying group protecting the carboxy group and, when present, the group protecting the hydroxy group, and if desired converting by methods known *per se* a penicillanic or cephalosporanic acid thus obtained into its alkali metal, alkaline earth metal or amine salt.

19. Process according to claim 18 in which a tri(lower)-alkylsilyl group is used as a protecting group for the carboxy radical, or hydroxy radical when present.

20. Process according to claim 18 or 19 in which a solution of a complex of a suitable organo-metal reagent, preferably n-butyllithium, and an N,N,N',N'-tetra-substituted-alkylene diamine, preferably N,N,N',N'-tetramethylethylenediamine, in an apolar solvent or solvent mixture is added to a solution or suspension of a heterocyclic compound of formula (III) specified in claim 18, X representing a hydrogen atom, in an apolar or slightly polar solvent, preferably toluene, at a low temperature, preferably −40° C. to −80° C., after which a solution of the isocyanate of formula (IV) or (V) as specified in claim 18 in toluene is introduced, followed by a treatment of the reaction mixture so obtained with water, and isolation of the product of formula (I) or (II) as specified in claim 1 from the reaction mixture by methods known *per se*.

21. Process for the preparation of compound of the formulae specified in claim 1, or alkali metal, alkaline earth metal or amine salts thereof, according to claim 18 substantially as described in any one of Examples I to XII.

22. Penicillanic and cephalosporanic acid derivatives of the general formulae specified in claim 1, and alkali metal, alkaline earth metal and amine salts thereof when prepared by the process claimed in any one of claims 18 to 21.

23. Pharmaceutical compositions comprising at least one penicillanic or cephalosporanic acid derivatives as claimed in any one of claims 1 to 17 or 22, or non-toxic alkali metal, alkaline earth metal or amine salt thereof, in association with a pharmaceutically acceptable carrier.

24. Pharmaceutical compositions according to claim 23 substantially as hereinbefore described with especial reference to Example XIII.

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